inhibitor PD98095 abrogated MET induced by GSK3b inhibition in MMs without altering cell survival or proliferation. These results demonstrate that Wnt signaling stabilizes b-catenin to facilitate MET in the MM and that MAPK/ERK signaling is also critical for this morphogenesis and further suggest that activation of the canonical Wnt signaling pathway (TCF) is responsible, at least in part, for cell survival and proliferation.

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Program/Abstract # 341

Wnt9b signals through the canonical β-catenin pathway to induce kidney tubules

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We are interested in the molecular regulation of mesenchymal to epithelial transition (MET) using the embryonic mouse kidney as a model system. Development of the mouse metanephric kidney begins around embryonic day 11 (E11.0). At this time the Wolffian duct branches to form the ureteric bud (UB), which invades the metanephric mesenchyme (MM) and secretes Wnt9b. Wnt9b induces the MM to undergo a MET resulting in tubule formation. We have previously shown Wnt9b is both necessary and sufficient for tubulogenesis. The mechanism through which Wnt9b elicits this response is currently unknown. To elucidate the cellular and molecular events downstream of Wnt9b we have performed an affymetrix microarray screen comparing MM from wild type and Wnt9b−/− animals at E11.5. Our results indicate that the canonical Wnt pathway is significantly affected (p-value=0.036 Fisher's exact test) in the Wnt9b−/− MM. Several canonical Wnt targets and regulators of canonical signaling are misregulated, including sFRP2, Fgf9, Fz2, Fz8, Tcf1 and Lef1, indicating that Wnt9b may be signaling through the canonical pathway. In support of this hypothesis, culturing Wnt9b−/− kidneys in the presence of LiClj, which acts by stabilizing β-catenin, is sufficient to rescue tubulogenesis. Our results indicate that Wnt9b signals canonically to regulate MET during development of the metanephric kidney.

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Program/Abstract # 342

Loss of β-catenin results in premature differentiation and extrusion of Wolffian duct epithelia

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Differentiation is the process by which tissues/organs take on their final, physiologically functional form. This process is mediated in part by the silencing of embryonic genes and the activation of terminal, differentiation gene products. Mammalian kidney development is initiated when the Wolffian duct branches and invades the overlying metanephric mesenchyme. The newly formed epithelial bud, known as the ureteric bud, will continue to branch ultimately differentiating into the collecting duct system and ureter. Here, we show that Hoxb7-Cre mediated removal of β-catenin from the mouse Wolffian duct epithelium leads to the premature expression of gene products normally associated with the differentiated kidney collecting duct system including Aquaporin-3 and the tight junction protein isoform ZO-1α+. Mutant cells also appear to be differentially adhesive and are extruded as intact epithelial cysts. Mutant cells do not initiate or maintain expression of genes necessary for normal branching morphogenesis leading to kidney aplasia and dysplasia. These data implicate a role forβ-catenin in maintaining cells of the Wolffian ducts and the duct derived ureteric bud/collecting duct system in an undifferentiated or precursor state.

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Withdrawn.

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Patterning of the arterial vascular tree in fetal mouse kidneys

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Renal vascularization is a dynamic process that requires highly coordinated interactions between vascular cells and the epithelial ureteric tree and nephrons. To examine the development of the arterial tree, we labeled fetal HoxB7-GFP kidneys with GSI-B4, a lectin that binds to endothelial cells. The ureteric bud and its derivatives were endogenously labeled with GFP. Three-dimensional confocal analysis of labeled kidneys indicated that the large arterial vessels are coordinately patterned with the developing ureteric tree (Conduah and Hyink, submitted manuscript). The arterial vessels do not physically contact the ureteric tree. The coordinated patterning of the large vessels and ureteric tree appear to be regulated by extracellular matrix tracts in embryonic day 13 (E13) to E18 kidneys. To examine this possibility, we examined the vasculature and ECM in mouse